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(54) HETEROCYCLE AMIDO ALKYLOXY SUBSTITUTED QUINAZOLINE DERIVATIVE AND USE THEREOF

HETEROCYCLISCHES AMIDOALKYLOXYSUBSTITUIERTES CHINAZOLINDERIVAT UND VERWENDUNG DAVON

DÉRIVÉ HÉTÉROCYCLIQUE DE QUINAZOLINE SUBSTITUÉ PAR UN AMIDO-ALKYLOXY ET SON UTILISATION

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- **CRAIG S. HARRIS, LAURENT F. HENNEQUIN, JASON G. KETTLE , OLIVIER A. WILLERVAL: "Selective alkylation of a 6,7-dihydroquinazoline", TETRAHEDRON LETTERS, vol. 46, no. 45, 26 September 2005 (2005-09-26), pages 7715-7719, XP002740887,**

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Description

Technical Field

[0001] This invention relates to a substituted quinazoline derivative. In certain exemplary embodiments, heterocycle amino alkyloxy substituted quinazoline derivatives and pharmaceutically acceptable salts thereof are provided. One or more derivative compunds can be used as active ingredient to inhibit the activity of receptor tyrosine kinase EGFR, and/or to reduce phosphorylation of the kinase on tyrosine residue contained in substrate and effectively improve and treat a variety of diseases (e.g. tumor) thus caused.

Background

[0002] Traditional chemotherapeutic drugs treat cancer by inhibiting DNA synthesis and/or inhibiting cell division. Practice shows that these compounds also have certain toxicity to normal cells. However, the molecular targeted therapies (MTTs) developed in the past one or two decades can greatly lower the toxicity of drugs to normal cells. Imatinib, which is used as therapy of Chronic Myeloid Leukemia (CML), has become one of the breakthrough milestones in the field (The Lancet Oncology, 2008, 600).

[0003] Epidermal growth factor receptor (EGFR/ErbB1/HER1) a transmembrane protein having a molecular weight of approximately 170 kD, is a member of receptor tyrosine kinase ErbB Family. This family includes members such as EbB2/ HER2/Neu, ErbB3/HER3, ERbB4/HER4 and the like. After a ligand that is similar to EGF (e.g. EGF and TGF-α) conjugates to the receptor, dimerization occurs, and thus activating a signaling pathway within a variety of downstream cells, e.g. PI3K/Akt, MAPK, signal transducers and activators of transcription (STAT), and the like. These signaling pathways are involved in the significant physiological processes, such as regulation, migration, cell death, cell growth, and the like. (Expet. Opin. Emerg. Drugs, 2010, 185).

[0004] Many studies have shown that a variety of tumor cells are directly related to over-expression of EGFR and over-expression of EGFR ligand (Curr. Drug Targets, 2001, 2, 117-133), The growth of multiple types of tumor cells can be effectively controlled by inhibiting the conjugation between EGFR and its ligand as well as activity of EGFR tyrosine kinase. There are a variety of drugs to inhibit EGFR for treating cancer currently in clinical trials. These cancers include lung cancer, colon cancer, gastric cancer, breast cancer, ovarian cancer, leukemia, prostate cancer, uterine cancer, pancreatic cancer, liver cancer, bladder cancer, renal cancer, thyroid cancer, brain cancer, head and neck cancer, and the like (Cell. Signal., 2010, 22, 984-1002).

[0005] The research and development of antitumor drugs against EGFR is mainly concentrated on the antibody drug and small molecule compounds that inhibit the tyrosine kinase receptor. The first generation of small molecule compounds are reversible kinase inhibitors, such as Astra-Zeneca's Gefitinib (US5,616,582), Roche's Erlotinib (US RE41,065) and GlaxoSmithKline's (GSK) Lapatinib (US6,391,874), and etc. The second generation of mall molecule compounds are irreversible inhibitors, such as Boehringer Ingelheim's BIBW2992 (Oncogene, 2008, 27, 4702-4711) and Pfizer's Neratinib (Cancer Res. 2004, 64, 3958-3965), which are in Phase III clinical trials. Conjugating with receptor kinase via covalent bonds, these compounds are better able to inhinit EGFR and related kinases, and demonstrate significantly higher inhibiting effectiveness, especially for cancer cells containing mutant receptor tyrosine kinases.

[0006] WO 02/18372 A1 and Harvis C.S. et al. Tetrahedron Letters, 46, 45 7715-7719 describe bicyclic heterocycles including quiquinazoline derivatives useful for treating tumor diseases of the lung and the respiratory tract.

[0007] CN 101 367 793 A describes EGFR inhibitory compounds for treating tumors.

[0008] The it has been difficult to develop therapeutic drugs that target EGFR due to the secondary mutations in EGFR that cause drug resistance, in clinical settings, it is difficult to choose the right drug because of the diversity of kinase mutations. However, [[the]] genetic testing and the diagnostic tools, developed in recent years, have facilitated selecting drugs more effectively. It has become an inevitable development in direction of molecular targeted cancer treatment in the past one or two decades that treating cancer patients having different mutations with different types of drugs is necessary. Therefore, the development of more innovative drug molecules, and that meet the medical need of different patients by providing more personalized cancer treatment drugs are desired.

Description of the invention

[0009] In one aspect of the invention, a heterocycle amino alkyloxy substituted quinazoline derivative, as defined in the appended claims, to inhibit EGFR and other receptor tyrosine kinases are provided.

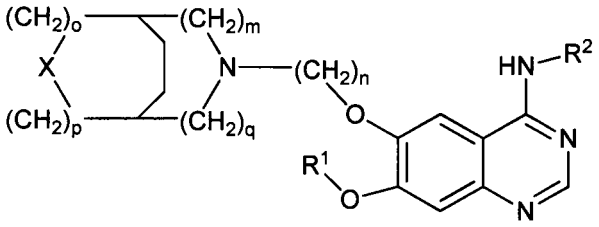
[0010] In another aspect of the invention, a bridged heterocycle amino alkyloxy substituted quinazoline derivative, as defined in the appended claims, to inhibit EGFR and other receptor tyrosine kinases are provided.

[0011] In another aspect of the invention, a pharmaceutical composition containing a heterocycle amino alkyloxy substituted quinazoline derivative and/or a pharmaceutically acceptable salt thereof are provided as active ingredients,

and applied to inhibit EGFR and other receptor tyrosine kinases.

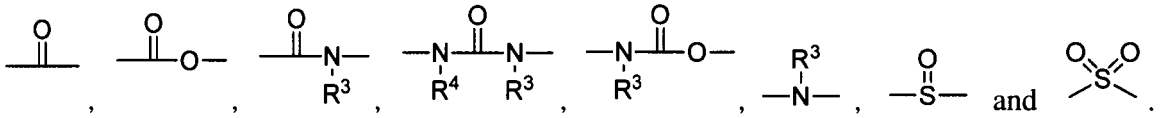
[0012] In another aspect of the invention, a pharmaceutical composition containing a heterocycle amido alkyloxy substituted quinazoline derivative and/or a pharmaceutically acceptable salt thereof are provided as active ingredients, and applied to prepare the drugs for cancer treatment.

[0013] In another preferred embodiment of a bridged heterocycle amino alkyloxy substituted quinazoline derivative, the active ingredients of the compounds are as represented by Formula III-II:



FormulaIII- II

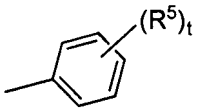
wherein m, o, p and q are integers each independently selected from from 0 to 6, e.g. 0, 1, 2, 3, 4, 5, and 6; and more preferably selected the integer from 0 to 4; n is selected from integers from 2 to 4, e.g. 2, 3 and 4; and
group X is selected from atom O, atom S, or one of the following groups:



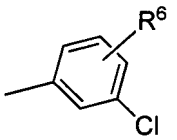
[0014] Group R^3 and group R^4 are respectively and independently selected from one of hydrogen, acyl, sulfonyl, unsubstituted C1-C6 alkyl, unsubstituted C3-C7 cycloalkyl, unsubstituted phenyl, and unsubstituted aromatic heterocyclyl.

[0015] Group R^1 is selected form the group of methyl, ethyl, deuterated ethyl, trifluoromethyl, methoxyethyl, cyclopropyl or cyclopropyl methyl.

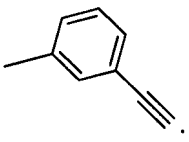
[0016] Group R^2 is phenyl substituted by one or several from halogen, alkyl, alkenyl and alkynyl, or aromatic heterocyclyl substituted by one or several from halogen, alkyl, alkenyl and alkynyl; and the more preferred group is



wherein t equals to 1 or 2, each group R^5, which may be same or different, is independently from fluorine, chlorine, bromine, cyano, and C2-C4 alkynyl, and the group



wherein R^6 is one from fluorine, chlorine, bromine, cyano and alkynyl, and the group



[0017] According to the understanding of a skilled person in the art, since one or more asymmetric carbon atoms can be formed, certain of the compounds set forth as FormulaIII-II of the invention, will present the optically active or racemic forms, or the geometrical isomers (e.g. E- and Z-isomer). Therefore, the Formulas described herein also include the

optically active or racemic forms, or the geometrical isomers. These optically active or racemic forms can be produced, e.g., by the synthesis with optical rotation raw materials, the by biotransformation, or by the separation, e.g., using a separation column.

[0018] The various heterocycle amino alkyloxy substituted quinazoline derivatives of the present invention, as well as pharmaceutical composition produced by all kinds of pharmaceutic adjuvants, addition agents or carriers in favor of the pharmaceutical composition administered, such as, but not limited to aqueous solution injection, powder injection, pills, pulvis, tablets, patches, suppository, emulsion, creme, gels, granular formulation, capsule, aerosol, spraying agent, powder spray, sustained release, controlled release formulations, and the like. These pharmaceutic adjuvants not only can usually be used in all kinds of formulations such as, but not limited to one or any combination of, isotonic agent, buffer solution, flavouring agent, antiseptic, bacteriostatic agent, excipient, loading agent, adhesive, disintegrant, lubricant and etc., but also selected in order to adapt with the choice of the material used, such as emulsifier, solubilizer, bacteriostatic agent, analgetic, antioxidant and etc. Such kind of adjuvants can effectively enhance stability and solubility of compounds contained in composition or alter release and absorption rate of compounds, thus improving metabolism of compounds of the invention in vivo and strengthening drug effect. Additionally, adjuvants, such as, but not limited to gelatin, albumin, chitosan, polyether and polyester polymers which are such as, but not limited to polyoxyethylene, polyurethane, polycarbonate and copolymers can be used to achieve a particular purpose or mode of administration, such as sustained release, controlled release and pulsed release. The main performance of the said "in favor of administration" includes, but not limited to, improved treatment effect and bioavailability, lower toxic and side effects, and higher patient adaptability. Pharmaceutic adjuvants, addition agents or carriers may vary from about 5% to about 99% by weight of the total pharmaceutical composition.

[0019] A pharmaceutical composition containing, by weight, 1%-95% active ingredients of a heterocycle amino alkyloxy substituted quinazoline derivative and pharmaceutically acceptable salt thereof of the present invention was administered to a subject. The effective dosage of the active ingredients was comfirmed according to the body weight, or according to the actual situation of the organisms and disease thereof. The times and dosage could also be adjusted, such as twice or more per day. According to the formulation, the effective therapeutic dosage administrated would still be different.

[0020] The present invention provides a pharmaceutical composition including one or several of the following compounds and/or pharmaceutically acceptable salts thereof as active ingredients:

Compound 11: 4-(3'-chloro-4'-fluorophenylamino)-6-[2-(8-oxa-3-azabicyclo[3.2.1]octane-3-yl)-oxethyl]-7-methoxyquinazoline

Compound 12: 4-(3'-chloro-4'-fluorophenylamino)-6-[3-(8-oxa-3-azabicyclo[3.2.1]octane-3-yl)-propoxy]-7-methoxyquinazoline

Compound 13: 4-(3'-chloro-4'-fluorophenylamino)-6-[2-(3-oxa-8-azabicyclo [3.2.1]octane-8-yl)-oxethyl]-7-methoxyquinazoline

Compound 16: 4-(5'-chloro-2'-fluorophenylamino)-6-[3-(3-oxa-8-azabicyclo [3.2.1] octane-8-yl)-propoxy]-7-methoxyquinazoline

Compound 42: 4-(3'-ethynylphenylamino)-6-[3-(3-oxa-8-azabicyclo[3.2.1]octane-8-yl)-propoxy] -7 -methoxyquinazoline

Compound 93: 4-(3'-chloro-4'-fluorophenylamino)-6-[3-(8-oxa-3-aza-azabicyclo[3.2.1]octane-3-yl)-propoxy]-7 -methoxyquinazoline

[0021] All kinds of heterocycle amido alkyloxy substituted quinazoline derivative provided in the invention as well as various drugs made from heterocycle amido alkyloxy substituted quinazoline derivatives can inhibit receptor tyrosine kinase EGFR of ErbB family. Besides, they can also inhibit Her2, Her3, Her4 and other receptor tyrosine kinase related to cancer, such as Vascular-endothelial Growth Factor Receptor (VEGFR), Fibroblast Growth Factor Receptor (FGFR), Platelet-derived Growth Factor Receptor (PDGFR), Insulin and insulin-like Growth Factor-1 Receptor (IGF-1R), and Hepatocyte Growth Factor Receptor (HGFR or c-MET), and reduce the phosphorylation of these tyrosine kinases on tyrosine contained in substrates, and can be applied to treat various cancer patients. These cancers include, but not limited to, cancer of lungs, intestine, stomach, mammary gland, ovary, prostate, uterus, pancreas, liver, bladder, kidney, thyroid gland, brain, head and neck, leukemia, and etc., which are directly related to over-expression of receptor tyrosine kinase.

[0022] According to the understanding of a skilled person in the art, some compounds, indicated in the FormulaIII-II of the invention, have a polycrystalline phenomenon. Thus, the types of inhibitory effect of these compounds on the

receptor tyrosine kinase of ErbB family are also included within the scope of the invention. Furthermore, those compounds in form of tautomer are also included in the scope of the invention. Terminology used in the present invention has the same meaning with general concepts.

[0023] The term "substituted," as used herein, refers to substitution at a position with one or any combination of groups including, but not limited to, hydroxyl, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C7 cycloalkyl, C1-C8 alkoxy, amine, C1-C8 alkylamino, di (C1-C8) alkylamino, C1-C8 alkylthio and halogen, and preferably selects from hydroxyl, methoxyl, amino, methylamino, dimethylamino, methylthio, halogen, and etc.

[0024] The term "halogen," as used herein, refers to group selected from fluorine, chlorine, bromine and iodine and any combination thereof.

[0025] The term "C," as used herein, should be understood as carbon or carbon atom. "C1-C3" , "C1-C6" , "C1-C8" , "C2-C8" , "C2-C4" , "C3-C7" and "C6-C10" stand for carbon atom and its number beared in groups, the letter C refers to carbon atom and the numeric behind it is a positive integer, e.g. 1, 2, 3, 4 or 5, which stands for the number of carbon atoms. Namely, C1 refers to a group bearing 1 carbon atom; C3 refers to a group bearing 3 carbon atoms; C1-C3 refers to a group of groups bearing 1-3 carbon atoms. Thus, the meaning of the expression above-mentioned and similar ones not listed herein can be understood by a skilled person in the art.

[0026] The term "acyl," as used herein, refers to a monovalent group derivated from the organic or inorganic oxyacid by loss of hydroxyl, such as, but not limited to, nitroxyl, sulfonyl, carbonyl, sulphinyl, alkanoyl, and etc. Typical alkanoyl is such as, but not limited to, formyl, ethanoyl, propiono, and etc.

[0027] The term "sulfonyl," as used herein, refers to functional group derivated from sulfoacid by loss of hydroxyl. It can be written as R-S $(=O)_2$-, wherein the substituted R is C1-C6 alkyl.

[0028] When the term "alkyl" as used herein, is a group or part of a group, it refers to straight-chain saturated aliphatic hydrocarbon group or with branched chain. The said alkyl of the invention should be understood as the saturated aliphatic hydrocarbon group bearing unsubstituted hydrogen atom, including the saturated aliphatic hydrocarbon group that the hydrogen atom is partially or wholly substituted by "deuterium (D)". For example, the methyl should be understood as one or several of $-CH_3$, $-CH_2D$, $-CHD_2$, $-CD_3$, and etc. The alkyl of the invention preferably selects from C1-C8 alkyl, such as, but not limited to, methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, tert-butyl, n-amyl, isoamyl, neoamyl, hexyl, and etc., and especially C1-C3 alkyl.

[0029] The term "cycloalkyl," as used herein, refers to saturated or partially saturated single-ring, condensed-ring, spiro aliphatic hydrocarbon cycloalkyl, and preferably selects from rings composed by 3-7 carbon atoms, such as, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, and etc.

[0030] The term "alkoxyl," as used herein, refers to (alkyl-O-) group, and preferably selects from C1-C6 alkoxyl, such as, but not limited to, methoxyl, ethyoxyl, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, and etc.

[0031] When the term "alkenyl," as used herein, is a group or part of a group, it refers to aliphatic hydrocarbon group, which may be either straight chain or branched chain, bearing one carbon-carbon double bond. The present invention selects C3-C8 alkenyl, and preferably selects from C3, C4 and C5 alkenyl. The examples of alkenyl group includes, but not limited to, allyl and 2-butenyl.

[0032] When the term "alkynyl," as used herein, is a group or part of a group, it refers to aliphatic hydrocarbon group, which may be either straight chain or branched chain, bearing one carbon-carbon triple bond. The present invention selects C2-C6 alkynyl, and preferably selects from C2, C3 and C4 alkynyl, such as, but not limited to, ethynyl, propargyl, 2-alkyne butyl, and etc.

[0033] When the term "aryl group," as used herein, is used independently or in combination, it refers to carbocyclic aromatic system bearing one or two rings, wherein the said rings can be fused together. The term "aryl group" such as, but not limited to aryl group of phenyl, naphthyl and tetralyl, preferably seleted from C6-C10 aryl group, and more preferably seleted from phenyl. The said "aryl group" also bears one or several substituted groups, such as, but not limited to C1-C6 alkyl, hydroxyl, halogen, haloalkyl, nitryl, cyano-perssad, C1-C6 alkoxyl and C1-C6 alkylamino.

[0034] The term "heterocyclic group," as used herein, refers to aromatic or non-aromatic heterocyclic group, wherein one or several rings contain hetero atom, e.g. oxygen, nitrogen, sulfur, and etc. Aromatic heterocyclic group, i.e. commonly referred to heteroaryl, preferably from 5-6 membered monocyclic aromatic or 9-10 membered bicyclic aromatic which bears 1, 2 or 3 atoms selected from nitrogen, oxygen and sulfur, such as, but not limited to furyl, pyridyl, 2-oxo-1,2-dihydropyridine, pyridazinyl, pyrimidyl, pyrazinyl, thienyl, isoxazolyl, oxazolyl, oxadiazol, imidazolyl, pyrryl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, 1,2,3- thiadiazole, benzodioxol, benzimidazolyl, indolyl, isoindolyl, 1,3-dioxo-isoindolyl, quinolyl, indazolyl, benzisothiazolyl, benzoxazolyl, and benzisoxazolyl, pyridylof is prefered. The said "heteroaryl" bears one or several substituting groups such as, but not limited to C1-C6 alkyl, hydroxyl, halogen, haloalkyl, nitryl, cyano, C1-C6 alkoxyl, C1-C6 alkylamino and etc.

[0035] The term "non-aromatic heterocyclic group," as used herein, refers to non-aromatic heterocyclic group which preferably bears 5-6 membered monocyclic or 8-10 membered bicyclic or tricyclic, and may bears 1, 2 or 3 atoms selected from nitrogen, oxygen and sulfur, such as, but not limited to morpholinyl, thiomorpholinyl, tetrahydropyranyl, 1,1-dioxo-thiomorpholinyl, piperidyl, 2-oxo- piperidyl, pyrrolidinyl, 2-oxo-pyrrolidinyl, piperazine-2-ketone, 8-oxa-3-aza-

bicyclic[3.2.1]octyl and piperazinyl. The said "non-aromatic heterocyclic group" also bears one or several substituted group such as, but not limited to C1-C6 alkyl, hydroxyl, halogen, haloalkyl, nitryl, cyano, C1-C6 alkoxyl and C1-C6 alkylamino.

[0036] The term "pharmaceutically acceptable salts," as used herein, refers to certain salts of the compounds of the invention can preserve orginial biological activity and are appropriate for medical use. These salts are such as metal salts, salts formed with proper organic base, and amine salts formed with proper acid. Metal salts are such as alkali metals and alkaline-earth metal salts, specifically calcium salt, magnesium salt or ammonium salt. The salts are formed with proper organic base such as methylamine, dimethylamine, piperidine, morpholine or 3-(2-hydroxyethyl) amine. The proper acids include inorganic and organic acids, such as, but not limited to acetic acid, benzene sulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethyl sulfonic acid, fumaric acid, gluconic acid, glutamic acid, hydrobromic acid, chlorhydric acid, isethionic acid, lactic acid, malic acid, maleic acid, mandelic acid, methanesulfonic acid, nitric acid, phosphoric acid, succinic acid, sulphuric acid, tartaric acid or p-toluenesulfonic acid, and etc, preferably from chlorhydric acid, hydrobromic acid, phosphoric acid or sulphuric acid, more preferably from chlorhydric acid.

[0037] The term "treatment," as used herein, refers to preventing from and reducing occurrence or development of diseases and enabling development or aggravation course of diseases to be inhibited, controlled, alleviated, meliorated, retarded, ceased, delayed or reversed. All kinds of indicators and concerning disease, disorder or pathological condition at the time of the described preservation and/or medication include alleviation or reduction of symptoms or complications, or cure or elimination of diseases, disorders or condition.

[0038] The term "drugs," as used herein, refers to compound, composition consisting of multiple compounds, traditional Chinese medicinal materials and the extracts thereof, the composition or the formulation consists of the single compound as and compounds and used in remedy of diseases, or composition or formulation with single compound as main active ingredient. It also refers to composition or formulation with a variety of compounds as active ingredients. "Drugs" should be understood not only as products approved and permitted by administrative organization established according to the law of a country, but also all kinds of material forms, containing the single compound as active ingredient, formed in the the processs to obtain the approval and permission for manufaction. The "formed" should be understood to obtain by means of chemical synthesis, biotransformation or purchasing.

[0039] The term "effective therapeutic dose," as used herein, refers to the dose, using the compounds as active ingredient, which can alleviate various symptoms pathologically. Generally, the dose delivered is determined according to body weight of organisms, e.g. a total dose of 0.05mg/kg-50mg/kg daily. According to actual situation of organism and its diseases, the dose and the delivery frequency may also be adjusted e.g. dividing more than twice a day, and giving a total dose of 0.05-0.5mg/kg, 0.6-1mg/kg, 1-10mg/kg, 11-25mg/kg, 26-40mg/kg or 41-50mg/kg. According to different types of formulation, the given dose should also be changed, e.g. 10mg/kg for ordinary tablet, or lower for controlled and sustained release formulation. The specific dose of heterocycle amido alkyloxy substituted quinazoline derivative and pharmaceutically acceptable salts of the present invention should be determined depending on the circumstances, such as mode of administration, route of administration, the state of patients when administrated, and pathological condition when treated.

[0040] The terms "Patient,"[[,]] "organism" or "animal" as used herein, refers to human, wild animal [[and]] or livestock. In certain aspects, wild animals are natural without artificial domestication. In certain aspects, livestock is an animal fed artificially to provide source of food, such as, but not limited to dog, mouse, hamster, pig, horse, rabbit, dairy cow, buffalo, bull, sheep, goat, geese and chicken. The subjected in certain aspects, a "patient" , "organism" or "animal" is preferably mammals, especially humans.

Drawings

[0041]

Fig.1 refers to body weight trends of nude mice.
Fig.2 refers to tumor volume growth trends of nude mice.

Examples

[0042] The present invention will be detailed described as follows. Examples of the invention are intended only to illustrate the invention, not to limit. Although the invention is illustrated in detail with reference of the preferred examples, a skilled person in the art can understand and find an identical or improved technical solution without departing from the scope of the claims.

[0043] In the following examples, unless otherwise specified, all temperature are expressed in centigrade degree (°C). Unless otherwise specified, all kinds of initiative raw materials and agents can be acquired commercialy, e.g. Sigma-Aldrich. These acquired raw materials and agents are directly used without any further purification.

[0044] Glassware was dried by oven and /or heating. The reaction was tracked by silicone-60 F254 plate (0.25mm, TLC). The analytic of thin-layer chromatography is spread out in proper solvent ratio (v/v).

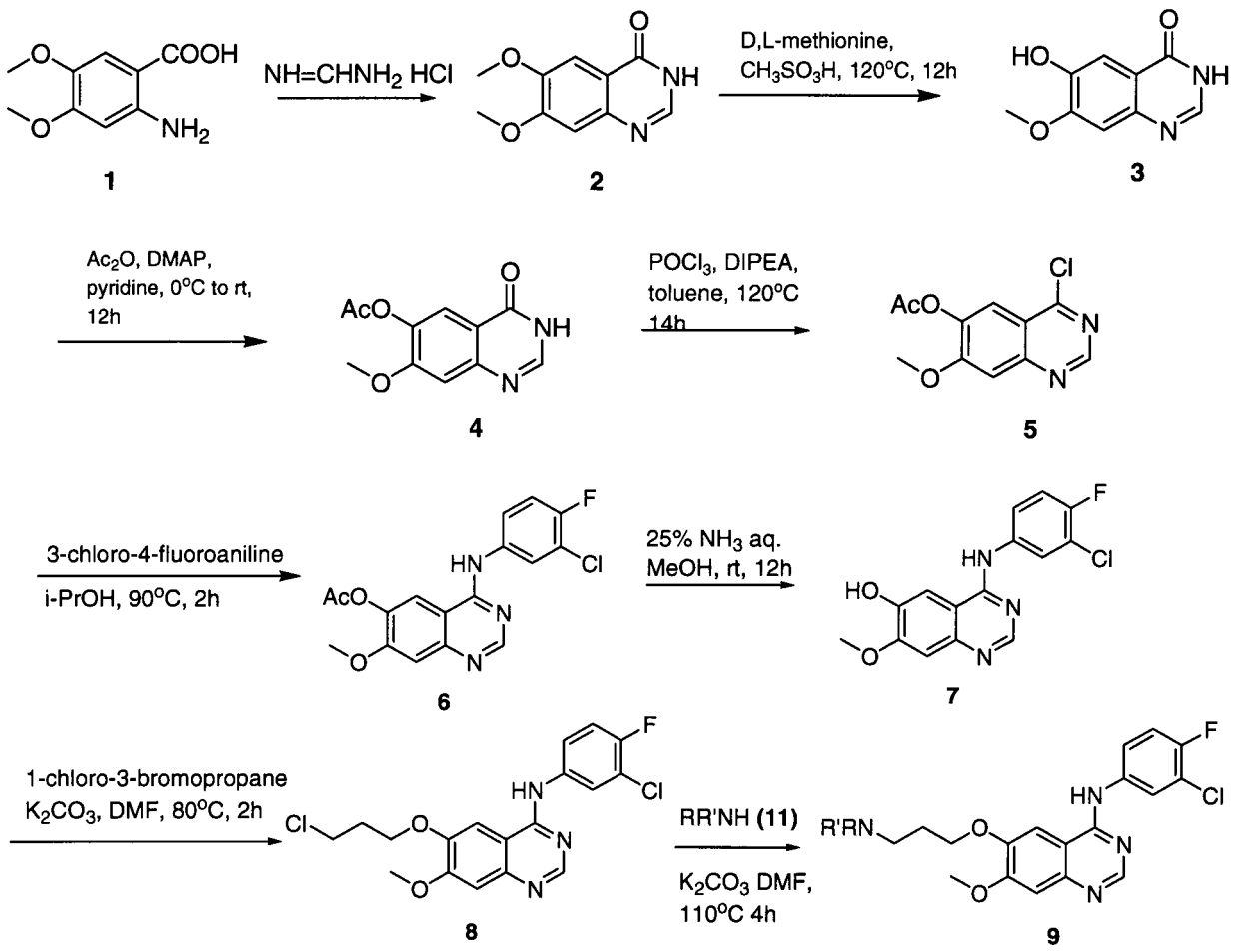
[0045] ^{1}H NMR spectra is determined by Bruker apparatus (400MHz). The chemical shift is expressed in ppm. Tetramethylsilane is applied to internal standard (0.00ppm). The expression of ^{1}H NMR are as follows: s=singlet, d=doublet, t=triplet, m=multiplet, br=broadened, dd=doublet of doublet. When giving a coupling constant, its unit is Hz.

[0046] The molecular weight of product is determined by LC/MS mass spectrometer, and the ionization method is ESI or APCI.

[0047] Various heterocycle amido alkyloxy substituted quinazoline derivative, pharmaceutically acceptable salts or its hydrates provided of the invention can be prepared by various public organic synthesis technologies.

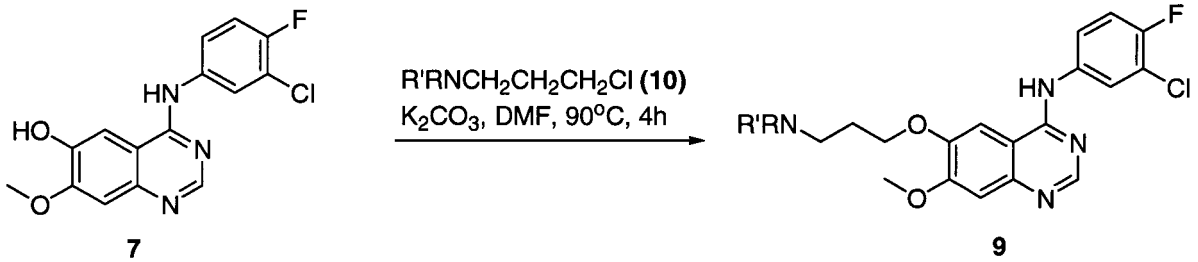
[0048] The preparation method provided in the present invention should be understood as necessary example for fully disclosure but not restriction to protective scope of the invention claims. Various compounds provided in the invention can be prepared by a skilled person in the art in the light of the examples listed in textbook, laboratory manual or the invention. The preparation of these compounds is also a part of generally indispensable skills which shall be mastered by a skilled person in the art, and can be completed under the guidance of the prior arts. Specifically, the preparation methods for some of the compounds provided in the invention is given as follows:

Synthetic scheme 1



Formula VI

Synthetic scheme 2



Formula VII

[0049] The following Examples are intended to illustrate the synthesis of compounds of the present invention only, but in these synthesis methods and without any restrictions. Compunds not listed in the following can also be prepared by the following synthetic routes and methods of the same, selecting the appropriate starting materials, and adjusting reaction conditions in the proper sense in somewhere necessary.

Synthetic scheme 1 (Formula VI)

[0050] The steps for the synthesis of intermediate compound 8:
Refering to the formula IV, and according to the formula VI, compound 7 (478mg, 1.5mmol), 1-bromo-3-chloropropane

(1.18g, 7.5mmol) and K_2CO_3 (1.05g, 7.5mmol) were added in into the flask prefilled with 3ml of DMF, heating it up to 90°C and keeping for 4 hours, and then cooling down to the room temperature. 15ml of water was added in, and the organic phases, extracted by ethyl acetate (20ml × 3), were combined. The combined organic phase was washed by water and saturated aqueous solution of Na_2CO_3 respectively. $MgSO_4$, used as desiccant, was added. The solvent was removed by rotary evaporator after the desiccant was removed by filtration. Using silica gel column (gradient elution using petroleum ether containing 20v/v%-80v/v% ethyl acetate as eluent) to separate the residue, and about 330mg of product 8 was obtained.

[0051] The steps for product 9 synthesis are as follows:

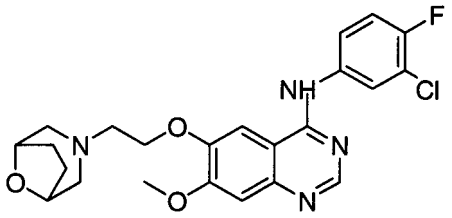
Compound 8 (96mg, 0.3mmol), amine 11 (RR'NH, 0.5mmol) and K_2CO_3 (0.21g, 1.5mmol) were added in into the flask prefilled with 3ml of DMF, the flask was heated up to 110°C and kept for 4 hours, and then cooling down to the room temperature. 10% aqueous solution of Na_2CO_3 (10ml) and ethyl acetate (20ml) was added in, and fully shaking to separate the organic phase. The separated organic phase was washed by saturated aqueous solution of Na_2CO_3. $MgSO_4$,used as desiccant, was added. The solvent was removed by rotary evaporator after the desiccant was removed by filtration. Using silica gel column or plate chromatography (using methylene dichloride containing 5v/v%-20v/v% methanol as eluent) to separate the residue, and the product 9 was obtained.

Synthetic scheme 2 (Formula VII)

[0052] Refering to the formula V, and according to the formula VII, compound 7 (96mg, 0.3mmol), 3-chloropropyl-substituted amine 10 (0.5mmol) and K_2CO_3 (0.21g, 1.5mmol) were added in into the flask prefilled with 3ml of DMF, heating it up to 90°C and keeping for 4 hours, and then cooling down to the room temperature. 10ml water was added in, and the organic phases, extracted by ethyl acetate (10ml × 3), were combined. The combined organic phase was washed by water and saturated aqueous solution of Na_2CO_3 respectively. $MgSO_4$, used as desiccant, was added. The solvent was removed by rotary evaporator after the desiccant was removed by filtration. Using silica gel column or plate chromatography (using methylene dichloride containing 5v/v%-20v/v% methanol as eluent) to separate the residue, and the product 9 was obtained.

Example 11

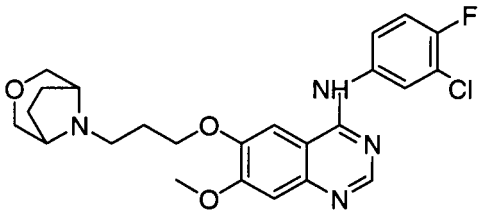
[0053] Using a procedure identical to that described in synthetic scheme 1, the compound 4-(3'-chloro-4'-fluorophenylamino)-6-[2-(8-oxa-3-azabicyclo[3.2.1]octane-3-yl)-oxethyl]-7-methoxyq uinazoline (2-C-M) was obtained.



^{1}H NMR ($CDCl_3$) 8.69(s, 1H), 7.99(q, J=2.4Hz, 1H), 7.61(m, 2H), 7.37(s, 1H), 7.20(t, J=8.8Hz, 1H), 4.41(t, J=6.8Hz, 2H), 4.04(s, 3H), 3.87(d, J=10.8Hz, 2H), 3.59(d, J=10.8Hz, 2H), 3.30(s, 2H), 2.95(m, 2H), 2.05(m, 4H). ES-MS (m/z): 459.1 (MH^+).

Example 12

[0054] Using a procedure identical to that described in synthetic scheme 1, the compound 4-(3'-chloro-4'-fluorophenylamino)-6-[3-(8-oxa-3-azabicyclo[3.2.1]octane-3-yl)-propoxy]-7-methoxyq uinazolin (3-C-O) was obtained.

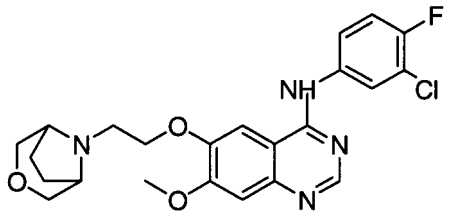


^{1}H NMR ($CDCl_3$) 8.69(s, 1H), 7.90(q, J=2.4Hz, 1H), 7.56(m, 1H), 7.20(t, J=8.8Hz, 1H), 7.12(s, 1H), 7.03(s, 1H), 4.33(s,

2H), 4.22(t, J=6.8Hz, 2H), 4.04(s, 3H), 2.67(d, J=10.7Hz, 2H), 2.57(t, J=6.8Hz, 2H), 2.38(d, J=10.9Hz, 2H), 2.10(m, 2H), 1.89(m, 4H). ES-MS (m/z): 473.2(MH^+).

Example 13

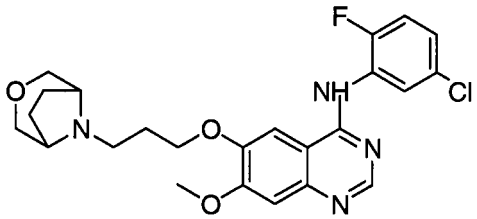
[0055] Using a procedure identical to that described in synthetic scheme 1, the compound 4-(3'-chloro-4'-fluorophenylamino)-6-[2-(3-oxa-8-azabicyclo[3.2.1]octane-8-yl)-oxethyl]-7-methoxyq uinazoline (2-C-O) was obtained.



^{1}H NMR (CDC13) 8.69(s, 1H), 7.92(q, J=2.4Hz, 1H), 7.56(m, 1H), 7.28(s, 1H), 7.21(t, J=8.8Hz,1H), 7.09(s, 1H), 4.34(d, J=2.4Hz, 2H), 4.28(t, J=6.0Hz, 2H), 4.04(s, 3H), 2.93(t, J=6.0Hz, 2H), 2.73(d, J=10.0Hz, 2H), 2.57(d, J=9.6Hz, 2H), 1.98(m, 2H), 1.90(m, 2H). ES-MS (m/z): 459.1(MH^+).

Example 16

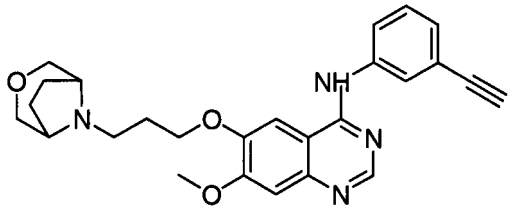
[0056] Using a procedure identical to that described in synthetic scheme 1, the compound 4-(5'-chloro-2'-fluorophenylamino)-6-[3-(3-oxa-8-azabicyclo[3.2.1]octane-8-yl)-propoxy]-7-methoxyq uinazolin (3-2-O) was obtained.



^{1}H NMR ($CDCl_3$) 8.78(m, 2H), 7.55(br, 1H), 7.32(br, 1H), 7.08(m, 3H), 4.33(s, 2H), 4.28(t, J=6.4Hz, 2H), 4.05(s, 3H), 2.81(d, J=9.6Hz, 2H), 2.61(m, 2H), 2.40(d, J=10.8Hz, 2H), 2.12(t, J=6.8Hz, 2H), 1.88(m, 4H). ES-MS (m/z): 473.0(MH^+).

Example 42

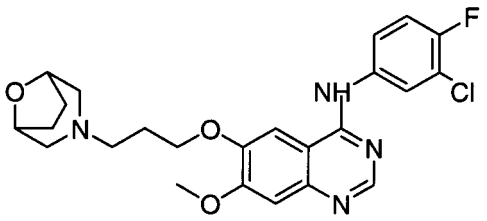
[0057] Using a procedure identical to that described in synthetic scheme 1, the compound 4-(3'-ethynylphenylamino)-6-[3-(3-oxa-8-azabicyclo[3.2.1]octane-8-yl)-propoxy]-7-methoxyquinazoli ne (3-4-O) was obtained.



^{1}H NMR ($CDCl_3$) 8.69(s, 1H), 8.04(s, 1H), 7.95(s, 1H), 7.85(d, J=7.6Hz, 1H), 7.38(t, J=8.0Hz, 1H), 7.30(s, 1H), 7.24(s, 1H), 4.36(m, 2H), 4.23(t, J=6.4Hz, 2H), 4.02(s, 3H), 3.11(s, 1H), 2.84(m, 2H), 2.71(m, 2H), 2.52(d, J=10.8Hz, 2H), 2.16(m, 2H), 2.09(m, 2H), 1.93(m, 2H). ES-MS (m/z): 444.9(MH^+).

Example 93

[0058] Using a procedure identical to that described in synthetic scheme 1, the compound 4-(3'-chloro-4'-fluorophenylamino)-6-[3-(8-oxa-3-aza-azabicyclo[3.2.1]octane-3-yl)-propoxy]-7-meth oxyquinazoline (3-C-M) was obtained.



^{1}H NMR ($CDCl_3$) 8.66(s, 1H), 8.24(m, 1H), 7.89(m, 1H), 7.52(s, 1H), 7.18(t, J=8.8Hz, 1H), 7.02(s, 1H), 4.26(t, J=6.8Hz, 2H), 4.03(s, 3H), 3.68(m, 2H), 3.56(m, 2H), 3.31(m, 2H), 2.84(m, 2H), 2.12(m, 2H), 1.98(m, 4H). ES-MS (m/z): 472.9(MH^+).

Example 119 Inhibitory effect on receptor tyrosine kinase EGFR of the compounds

[0059] The inhibitory effect on the receptor tyrosine kinase EGFR (purchased from Shanghai 3bio Technology Co., Ltd. , Lot No. 4018780925) of the compounds prepared in example 1-example 51 and example 53- example 99 was determined by in vitro testing, the specific testing methods were as follows:

Poly (Glu, Tyr) $_{4:1}$ was diluted into 100μg/ml by PBS without potassium. Enzyme label plate was coated with 37μl/well at 37°C overnight,
The liquid in the wells was removed. The plate was rinsed by T-PBS for 5 minutes, and dried at 37°C after repeated 3 times.

[0060] The testing sample was diluted to the concentration concerned by reaction buffer solution, and added into the wells of the coated enzyme label plate. The concentration diluted should realize 1.0000μg/ml, 0.1250μg/ml, 0.0156μg/ml, 0.00195μg/ml and 0.00024μg/ml in the 100μl reaction.

[0061] Adding in ATP solution (4μM of final concentration) diluted by reaction buffer solution,

[0062] Finally, the tyrosine kinase diluted by reaction buffer solution was added, and forming the reaction with 100μl total volume.

[0063] Meanwhile, negative control wells and enzyme-free control wells were prepared. The reaction was kept in the dark wet box for 1 hour at 37°C. The plate was rinsed by T-PBS for three times after the reaction ended, and blocked by 1% BSA 37% for 30min, and then, PY99 antibody (1:1000 diluted by 0.05% PBST with 1% BSA) was added in 100μl/well. After incubated at 37°C for 30 minutes, the plate was rinsed by T-PBS for three times, and the goat anti-mouse IgG marked with HRP (1mg/ml 1:1000 diluted by 0.05% PBST with 1% BSA) was then added in 100μl/well. After incubated at 37°C for 30 minutes, the plate was rinsed by T-PBS for three times.

[0064] Colorimetric solution OPD was added in 100μl/well for 20 minutes' reaction in the dark side at the room temperature. Colorimetric substrate solution OPD was the solution of 0.1mol/L citric acid-disodium hydrogen phosphate buffer (pH5.0) with 20mmol/L OPD and 12mmol/L H_2O_2 (freshly prepared when using).

[0065] 50μl of 2M H_2SO_4 (2mol/L sulfuric acid containing 0.1mol/L sodium sulfate) was added in to terminate the reaction, and the A_{492} value was read with adjustable wavelength micro plate enzyme-labeling instrument VERSAmax.

[0066] The inhibition rate of samples is calculated by the following formula:

$$\text{Inhibition rate of samples \%} = \left(1 - \frac{\text{OD value of compound} - \text{OD value of enzyme-free control hole}}{\text{OD value of negative control} - \text{OD value of enzyme-free control hole}}\right) \times 100\%$$

[0067] The results show that the compounds of the invention possesses strong inhibitory effect on activity of tyrosine kinase EGFR and the range of IC_{50} value is shown in Table 1. In Table 1, the value of IC_{50} larger than 1000nM is refered to "*", the value of IC_{50} between 100nM-1000nM is refered to "**", the value of IC_{50} between 10nM-100nM is refered to "***", and the value of IC_{50} between 0.1nM-10nM is refered to "****".

Table 1

Compound	IC_{50} (nM)é
Example 11	**
Example 12	***
Example 13	***

(continued)

Compound	IC_{50} (nM)é
Example 16	***
Example 42	**
Example 93	**

Example 120 anticancer effect of the compounds

[0068] The inhibitory effect on the cancer cells of the compounds prepared in Example 11-Example 13 was determined in vitro using cancer cells. The results are shown in table 2, and the specific detection methods are as follows:

1. Cell culture

[0069] Human lung cancer cells were (A549, purchased from Shanghai FuMeng Gene Bio-technology Co., Ltd.) cultured in DMEM containing 2m M/L- glutamine and 10% FBS, and inoculated in 96-well plate, 200μL/well and 2000 cells per well; the plate was preincubated for 24 hours under the condition of 5% CO_2 and 100% relative humidity at 37°C, allowing for cell adherence.

2. Compounds screening

[0070] When the cells adhered, the supernatant was removed, and 200μL drug-containing culture medium was added with different concentration of compounds into each well (in concentration of 20μg/ml, 12.5μg/ml, 6.25μg/ml, 3.125μg/ml, 1.5625μg/ml and 0.78125μg/ml), 3 mutiple wells were set up for each drug concentration as well as blank control (cell culture medium without cells), and drug-free control (with no drugs, filled with complete medium in equal amount only), cultured for 72 hours under the condition of 5% CO_2 incubator at 37°C (100% relative humidity).

3. Cell detection

[0071] After the culture ended, the supernatant was carefully removed, and adding 200μl DMEM culture medium containing 3% FBS with 500μg/ml MTT into each well, and culturing for 4 hours under the condition of 5% CO_2 incubator at 37°C (100% relative humidity). After the supernatant was discarded, 150μL DMSO was added in each well for solving, the GI_{50} value was mesured by detecting the absorbance in the 570nm wavelength.

4. Screening result

[0072] The compounds of the invention possess strong killing activity to human lungs cancer cell strain (A549), of which the GI_{50} is between 1μM and 60μM, and have lower killing effect on normal endothelium.

Table 2

Compound	GI_{50} (μM)
Example 11	26.6
Example 12	41.7
Example 13	28.8

Example 121 verifying the tumor inhibitory effect of the compounds of the disclosure on the nude mice

[0073] Refering the in vivo test methods recorded in "Antineoplastic Pharmacodynamics Guidelines" of SFDA, The inhibitory effect of 4-(3'-chloro-4'-fluorophenylamino)-6-[3-(2-oxa-6-azaspiro[3.4]octane-6-yl)-propoxy]-7-methoxy-quinazoline (hereinafter referred to as Compound C) on the tumor of nude mice was evaluated.

[0074] After digesting and detaching the monolayer-cultured human lungs cancer cell strain A549 (purchased from Shanghai FuMeng Gene Bio-technology Co., Ltd.), cells were collected and resuspended in the serum-free culture medium, and the concentration was adjusted to be 2×10^6/0.2mL. 0.2mL cell suspension was taken by injector and transplanted under the skin of square scapula behind left armpit of nude mice, 0.2mL for each mouse. The tumor volume was measured every 2 or 3 days. The nude mice bearing tumors which rapidly grew without any diabrosis were selected

after two weeks. Under the condition of asepsis, the tumors were removd, and cut into tumor tissue with the diameter approximal 2-3mm, and then inoculate the tissue under the skin of square scapula behind left armpit of nude mice by trocar. After repetition in three generations, the nude mice received administration randomly in groups excluding the ones bearing too large or too small tumors, when the tumor grew to be about 100mm^3 in volume.

[0075] The selected animals were 6-week old BALB/C nude mice. The male mice were 20-22g in weight and provided by Shanghai Laboratory Animal Center (SIPPR BK) (production permit No. SCXK (Hu) 2008-0016). The experimental period was totally 111 days.

[0076] The experiment was randomly divided into 2 groups, the negative control group consisting of 12 mice (solvent administration only) and treatment group consisting of 12 mice (compound C, 100mg/kg).

[0077] Ethanol was used as cosolvent to promote dissolution of compound C, adding 0.5w/v% carboxymethyl cellulose to form suspension with a 0.5% final concentration of carboxymethyl cellulose and a 10w/v% final concentration of ethanol, and then, using ultrasound to form uniform suspension. The dosage for intragastric administration was 0.1ml/10g, and the negative control group was only subjected to the same solvent. On the first day of experiment, compound C was given 100mg/kg in the morning and in the evening respectively, and afterwards, 100mg/kg was given in every morning only. The negative control group was only given 0.1ml/10g of 10v/v% ethanol 0.5w/v% carboxymethyl cellulose in every morning.

Experimental evaluation:

[0078] Index: observing state of animals and measuring body weight daily; measuring tumors by calipers every two days. Sacrifice the animal in 24 hours after the last administration and measure the volume and size of tumor. Dissecting the animal and removing the tumor; weighing the tumor and nude mice; and then, drawing the curves of tumor volume and growth, nude mouse weight, tumer inhibition rate and animal death rate.

[0079] Tumor diameter measurement is used to observe the antitumor effect of the test substances dynamicly. The formula for tumor volume (TV) calculation is:

$v = 0.5 \times a \times b^2$ (mm^3); wherein, a and b stand for length and width respectively.

[0080] The relative tumor volume (RTV) is calculated according to the measurement result; RTV=Vt/V0, wherein V0 is the tumor volume measured at the beginning of administration (i.e.d0) and Vt is the tumor volume at each measurement.

[0081] The index to evaluate antitumor activity is relative tumor proliferation rate T/C (%)+w'pF\u001E[.o:e\u001F^0

$$T/C\ \% = \frac{TRTV}{CRTV} \times 100\%$$

[0082] In the above formula, TRTV: RTV of treatment group, CRTV: RTV of negative control group.

$$\text{Tumor growth inhibition rate} = \frac{\textit{Average tumor weight of administration group} - \textit{average tumor weight of negative control group}}{\textit{Average tumor weight of negative control group}} \times 100\%$$

[0083] The experiment was started after nude mice adapt to the environment of laboratory. During the whole experiment process, each group of planted nude mice behaved reduced activity, slightly reduced food intake, and normal drinking. About 4 days after administration, the activity of nude mice returned to normal gradually, and the food intake and the drinking returned to normal. Comparing with the control group, the body weight of the nude mice of the treatment group (compound C) is consistent fluctuation. The results are shown in Fig.1.

[0084] After plantation, the formation of solid tumors can be touched in each nude mice group. At the same time in two days interval, the long diameters and the short diameters of the tumor were mearsured, and then, the volume of tumor is calculated accordingly. With the experiment proceeding, the tumor volume of the control group grows rapidly, and meanwhile the tumor volume of the treatment group grows relatively slowly. Two weeks after administration, the tumor volume and size of the treatment group is significantly less than the control group ($p<0.05$), and shown a statistically significant difference. The results are shown in Fig.2.

[0085] The nude mice were sacrificed on the 21st day after administration, and then, the tumors were removed and weighed. The average tumor weight of the treatment group is less than the negative group ($P<0.05$), and shown a statistically significant difference. According to the tumor volume and the tumor weight, the T/C% and the tumor inhibition rate are calculated. The results are shown in the table.

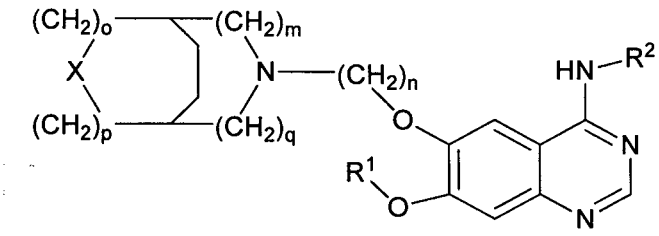
Table Inhibitory effects on tumors with nude mice

	Dose	Tumor volume (mm^3)	RTV	T/C %	Tumor mass (g)	Tumor inhibition rate (%)
Negative group		984.4±315.8	10.52±3.92	100	1.05±0.42	0
Treatment group	100mg/kg	515.4±388.0**	4.57±2.11**	43.44	0.55±0.43*	47.62

* refers to the comparison with the Negative group, $p<0.05$; ** refers to the comparison with the Negative group, $p<0$.

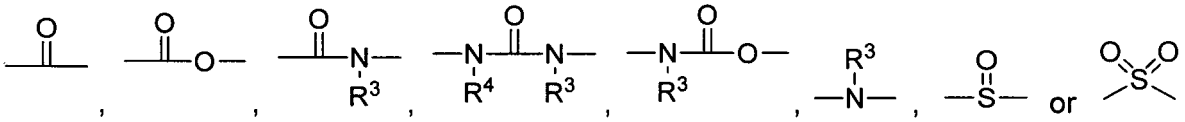
Claims

1. A heterocycle amino alkyloxy substituted quinazoline derivative as represented in Formula III-II:



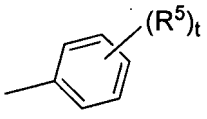
Formula III- II

wherein m, o, p and q are integers each independently selected from 0 to 6; n is an integer from 2 to 4;
group X is selected from O, S,

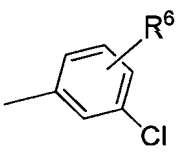


and wherein each of group R^3 and group R^4 is independently selected from any one of hydrogen, acyl, sulfonyl, unsubstituted C1-C6 alkyl, unsubstituted C3-C7 cycloalkyl, unsubstituted phenyl, and unsubstituted aromatic heterocyclyl;
group R^1 is selected from methyl, ethyl, deuterated ethyl, trifluoromethyl, methoxyethyl, cyclopropyl or cyclopropyl methyl;
group R^2 is selected from phenyl bearing one or several substituents selected from halogen, alkyl, alkenyl and alkynyl, or aromatic heterocyclyl bearing one or several substituents selected from halogen, alkyl, alkenyl and alkynyl.

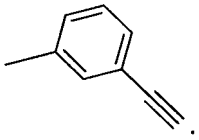
2. The heterocycle amino alkyloxy substituted quinazoline derivative according to claim 1, wherein the said group R^2 is selected from the group



and wherein, t equals to 1 or 2; each group R^5, which may be same or different, is independently selected any one from fluoro, chloro, bromo, cyano, and C2-C4 alkynyl; or the group



and wherein group R^6 is selected from fluoro, chloro, bromo, cyano and alkynyl; or the group



3. A heterocycle amino alkyloxy substituted quinazoline derivative selected from the group consisting of:

Compound 11: 4-(3'-chloro-4'-fluorophenylamino)-6-[2-(8-oxa-3-azabicyclo[3.2.1]octane-3-yl)-oxethyl]-7-methoxyquinazoline
Compound 12: 4-(3'-chloro-4'-fluorophenylamino)-6-[3-(8-oxa-3-azabicyclo[3.2.1]octane-3-yl)-propoxy]-7-methoxyquinazoline
Compound 13: 4-(3'-chloro-4'-fluorophenylamino)-6-[2-(3-oxa-8-azabicyclo [3.2.1]octane-8-yl)-oxethyl]-7-methoxyquinazoline
Compound 16: 4-(5'-chloro-2'-fluorophenylamino)-6-[3-(3-oxa-8-azabicyclo [3.2.1] octane-8-y)-propoxy]-7-methoxyquinazoline
Compound 42: 4-(3'-ethynylphenylamino)-6-[3-(3-oxa-8-azabicyclo[3.2.1]octane-8-yl)-propoxy]-7 -methoxy-quinazoline
Compound 93: 4-(3'-chloro-4'-fluorophenylamino)-6-[3-(8-oxa-3-aza-azabicyclo[3.2.1]octane- 3-yl)-propoxy]-7-methoxyquinazoline.

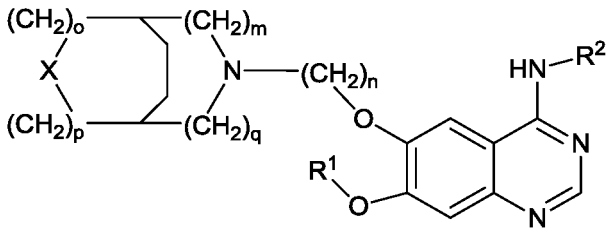
4. The heterocycle amino alkyloxy substituted quinazoline derivative or the pharmaceutically acceptable salt thereof as defined in any one of claims 1-3 for use in the treatment of a cancer selected from the group consisting of one or any combination of lung cancer, intestinal cancer, stomach cancer, mammary gland cancer, ovarian cancer, prostate cancer, uterine cancer, pancreatic cancer, liver cancer, bladder cancer, kidney cancer, thyroid gland cancer, brain cancer, head and neck cancer, and leukemia.

5. A pharmaceutical composition comprising a heterocycle amino alkyloxy substituted quinazoline derivative or a pharmaceutically acceptable salt thereof as defined in claims 1-3 as an active ingredient.

6. The pharmaceutical composition according to claim 5, wherein the said quinazoline derivative is selected from one or any combination of compounds 11, 12, 13, 16, 42 and 93 or the pharmaceutically acceptable salts thereof.

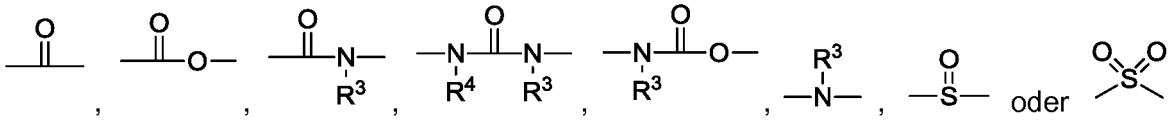
Patentansprüche

1. Heterocycloaminoalkyloxy-substituiertes Chinazolinderivat wie in Formel III-II wiedergegeben:



Formel III-II

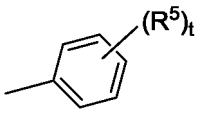
wobei m, o, p und q ganze Zahlen sind, die jeweils unabhängig aus 0 bis 6 ausgewählt sind;
n eine ganze Zahl von 2 bis 4 ist;
Gruppe X aus O, S,



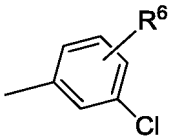
oder

ausgewählt ist,
und wobei jede von Gruppe R^3 und Gruppe R^4 unabhängig aus einem von Wasserstoff, Acyl, Sulfonyl, unsubstituiertem C1-C6-Alkyl, unsubstituiertem C3-C7-Cycloalkyl, unsubstituiertem Phenyl und unsubstituiertem aromatischem Heterocyclyl ausgewählt ist;
Gruppe R^1 aus Methyl, Ethyl, deuteriertem Ethyl, Trifluormethyl, Methoxyethyl, Cyclopropyl oder Cyclopropylmethyl ausgewählt ist;
Gruppe R^2 aus Phenyl, das einen oder mehrere Substituenten, ausgewählt aus Halogen, Alkyl, Alkenyl und Alkinyl, trägt, oder aromatischem Heterocyclyl, das einen oder mehrere Substituenten, ausgewählt aus Halogen, Alkyl, Alkenyl und Alkinyl, trägt, ausgewählt ist.

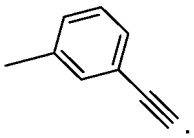
2. Heterocycloaminoalkyloxy-substituiertes Chinazolinderivat gemäß Anspruch 1, wobei die Gruppe R^2 ausgewählt ist aus der Gruppe



und wobei t gleich 1 oder 2 ist; jede Gruppe R^5, welche gleich oder unterschiedlich sein kann, unabhängig aus einem von Fluor, Chlor, Brom, Cyano und C2-C4-Alkinyl ausgewählt ist; oder der Gruppe



und wobei Gruppe R^6 aus Fluor, Chlor, Brom, Cyano und Alkinyl ausgewählt ist; oder der Gruppe



3. Heterocycloaminoalkyloxy-substituiertes Chinazolinderivat ausgewählt aus der Gruppe bestehend aus:

Verbindung 11: 4-(3'-Chlor-4'-fluorphenylamino)-6-[2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-oxethyl]-7-methoxychinazolin
Verbindung 12: 4-(3'-Chlor-4'-fluorphenylamino)-6-[3-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-propoxy]-7 -methoxychinazolin
Verbindung 13: 4-(3'-Chlor-4'-fluorphenylamino)-6-[2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-oxethyl]-7-methoxychinazolin
Verbindung 16: 4-(5'-Chlor-2'-fluorphenylamino)-6-[3-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-propoxy]-7 -methoxychinazolin
Verbindung 42: 4-(3'-Ethinylphenylamino)-6-[3-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-propoxy]-7 -methoxychinazolin
Verbindung 93: 4-(3'-Chlor-4'-fluorphenylamino)-6-[3-(8-oxa-3-aza-azabicyclo[3.2.1]octan-3-yl)-propoxy]-7-methoxychinazolin.

4. Heterocycloaminoalkyloxy-substituiertes Chinazolinderivat oder das pharmazeutisch verträgliche Salz davon wie in einem der Ansprüche 1-3 definiert zur Verwendung bei der Behandlung einer Krebserkrankung ausgewählt aus der Gruppe bestehend aus einem oder einer beliebigen Kombination von Lungenkrebs, Darmkrebs, Magenkrebs, Brustdrüsenkrebs, Eierstockkrebs, Prostatakrebs, Gebärmutterkrebs, Bauchspeicheldrüsenkrebs, Leberkrebs, Blasenkrebs, Nierenkrebs, Schilddrüsenkrebs, einer Krebserkrankung des Gehirns, Kopf- und Halskrebs, und Leukämie.

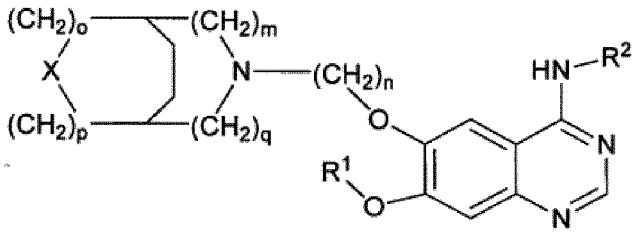
5. Pharmazeutische Zusammensetzung umfassend ein Heterocycloaminoalkyloxy-substituiertes Chinazolinderivat

oder ein pharmazeutisch verträgliches Salz davon wie in den Ansprüchen 1-3 definiert als einen Wirkstoff.

6. Pharmazeutische Zusammensetzung gemäß Anspruch 5, wobei das Chinazolinderivat aus einer oder einer beliebigen Kombination der Verbindungen 11, 12, 13, 16, 42 und 93 oder den pharmazeutisch verträglichen Salzen davon ausgewählt ist.

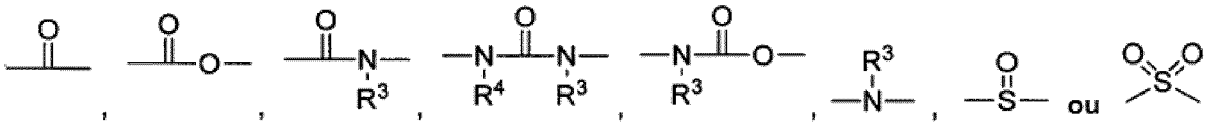
Revendications

1. Dérivé hétérocyclique de quinazoline à substitution aminoalkyloxy ainsi que représenté dans la formule III-II :



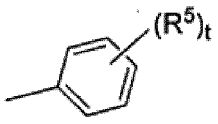
Formule III-II

dans laquelle m, o, p et q sont des entiers choisis chacun indépendamment de 0 à 6;
n est un entier de 2 à 4 ;
le groupe X est choisi parmi O, S,

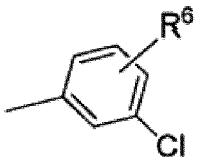


et dans laquelle chaque groupe R^3 et groupe R^4 est choisi indépendamment parmi l'un quelconque d'un hydrogène, acyle, sulfonyle, alkyle en C1 à C6 non substitué, cycloalkyle en C3 à C7 non substitué, phényle non substitué et hétérocyclyle aromatique non substitué ;
le groupe R^1 est choisi parmi un méthyle, éthyle, éthyle deutéré, trifluorométhyle, méthoxyéthyle, cyclopropyle ou cyclopropylméthyle ;
le groupe R^2 est choisi parmi un phényle portant un ou plusieurs substituants choisis parmi un halogène, alkyle, alcényle et alcynyle, ou un hétérocyclyle aromatique portant un ou plusieurs substituants choisis parmi un halogène, alkyle, alcényle et alcynyle.

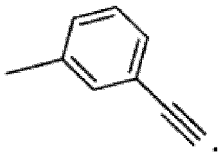
2. Dérivé hétérocyclique de quinazoline à substitution aminoalkyloxy selon la revendication 1, dans lequel ledit groupe R^2 est choisi dans le groupe



et dans lequel, t est égal à 1 ou 2 ; chaque groupe R^5, qui peut être identique ou différent, est choisi indépendamment l'un quelconque parmi un fluoro, chloro, bromo, cyano et alcynyle en C2 à C4 ; ou le groupe



et où le groupe R^6 est choisi parmi un fluoro, chloro, bromo, cyano et alkyle ; ou le groupe



3. Dérivé hétérocyclique de quinazoline à substitution aminoalkyloxy choisi dans le groupe constitué de :

Composé 11 : 4-(3'-chloro-4'-fluorophénylamino)-6-[2-(8-oxa-3-azabicy-clo[3.2.1]octan-3-yl)-oxéthyl]-7-méthoxyquinazol ine
Composé 12 : 4-(3'-chloro-4'-fluorophénylamino)-6-[3-(8-oxa-3-azabicy-clo[3.2.1]octan-3-yl)-propoxy]-7-méthoxyquinazoline
Composé 13 : 4-(3'-chloro-4'-fluorophénylamino)-6-[2-(3-oxa-8-azabicy-clo[3.2.1]octan-8-yl)-oxéthyl]-7-méthoxyquinazol ine
Composé 16 : 4-(5'-chloro-2'-fluorophénylamino)-6-[3-(3-oxa-8-azabicy-clo[3.2.1]octan-8-yl)-propoxy]-7-méthoxyquinazoline
Composé 42 : 4-(3'-éthynylphénylamino)-6-[3-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-propoxy]-7-méthoxyquinazol ine
Composé 93 : 4-(3'-chloro-4'-fluorophénylamino)-6-[3-(8-oxa-3-aza-azabicy-clo[3.2.1]octan-3-yl)-propoxy]-7-méthoxyquinazoline.

4. Dérivé hétérocyclique de quinazoline à substitution aminoalkyloxy ou sel pharmaceutiquement acceptable de celui-ci ainsi que défini dans l'une quelconque des revendications 1 à 3 destiné à être utilisé dans le traitement d'un cancer choisi dans le groupe constitué de l'un ou d'une quelconque combinaison d'un cancer du poumon, cancer de l'intestin, cancer de l'estomac, cancer de la glande mammaire, cancer de l'ovaire, cancer de la prostate, cancer de l'utérus, cancer du pancréas, cancer du foie, cancer de la vessie, cancer du rein, cancer de la glande thyroïde, cancer du cerveau, cancer de la tête et du cou et leucémie.

5. Composition pharmaceutique comprenant un dérivé hétérocyclique de quinazoline à substitution aminoalkyloxy ou un sel pharmaceutiquement acceptable de celui-ci ainsi que défini dans les revendications 1 à 3 en tant que principe actif.

6. Composition pharmaceutique selon la revendication 5, dans laquelle ledit dérivé de quinazoline est choisi parmi l'un ou une quelconque combinaison des composés 11, 12, 13, 16, 42 et 93 ou de sels pharmaceutiquement acceptables de ceux-ci.

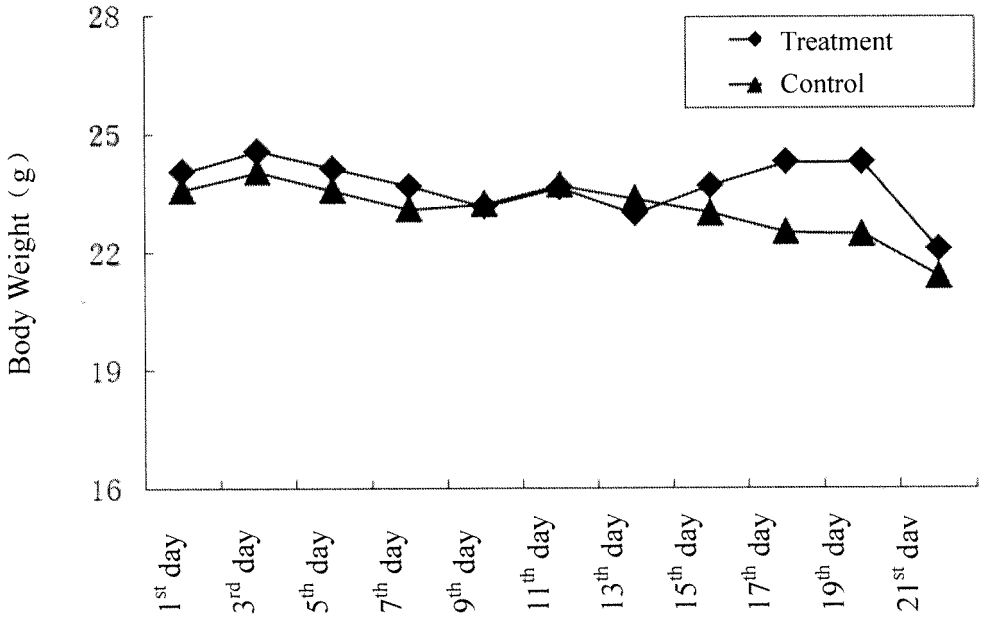

28
25
22
19
16
Body Weight（g）
Treatment
Control
1st day
3rd day
5th day
7th day
9th day
11th day
13th day
15th day
17th day
19th day
21st dav

Fig.1

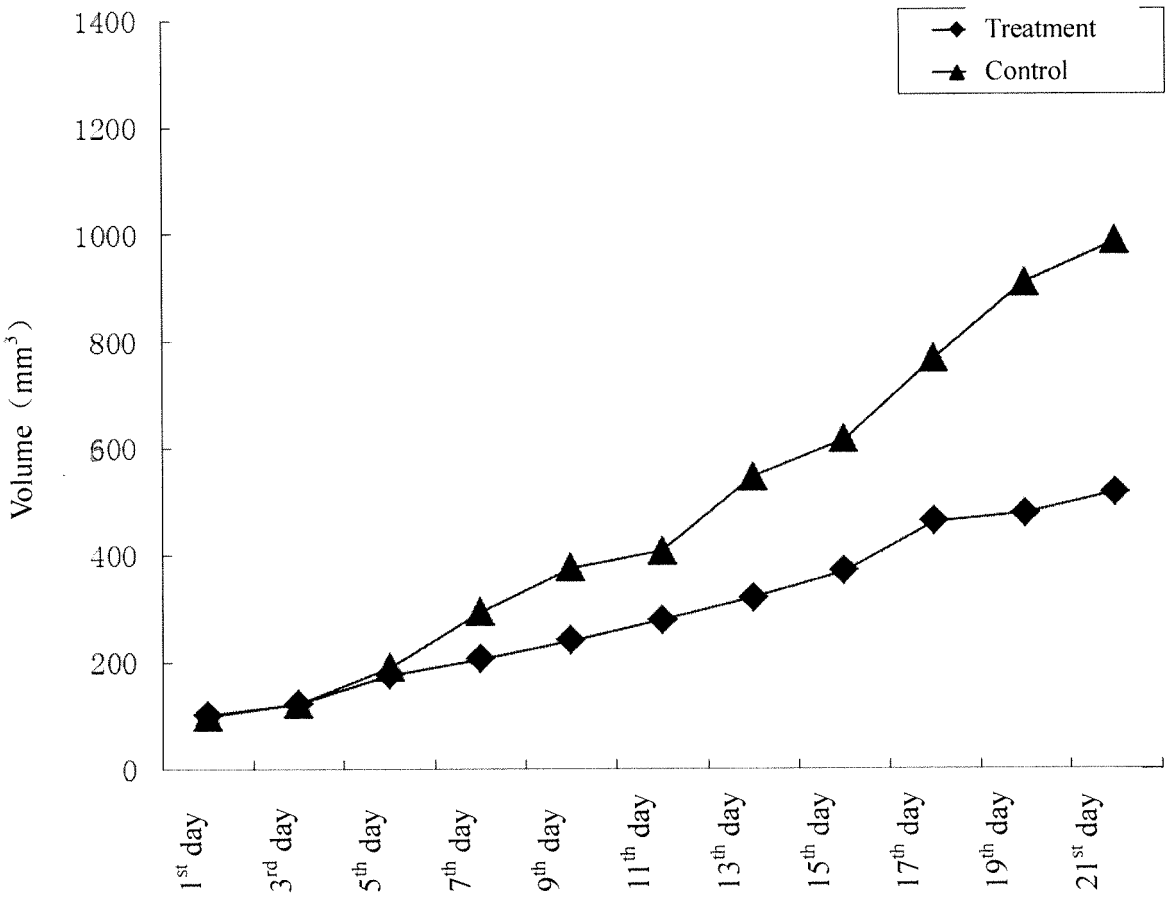

Treatment
Control
Volume（mm3）
1400
1200
1000
800
600
400
200
0
1st day
3rd day
5th day
7th day
9th day
11th day
13th day
15th day
17th day
19th day
21st day

Fig.2

REFERENCES CITED IN THE DESCRIPTION

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